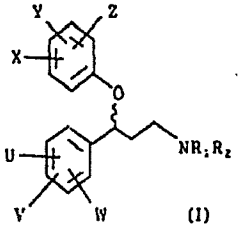
92-398487/48 B05 UYPE- 91.05.01
UNIV PENNSYLVANIA *WO 9219210-A2
91.05.01 91US-694346 (92.11.12) A61K

Novel serotonin re-uptake inhibitor cpds. - are antidepressants, also useful for imaging serotonin receptors when contg. radioactive halogen isotopes (Eng)

C92-176712 N(CA JP) R(AT BE CH DE DK ES FR GB GR IT LU MC NL SE)
Addnl. Data: KUNG H F
92.04.22 92WO-US03261

Substd. 3-phenoxy-3-phenylpropylamine derivs. of formula (I) and their salts are new:



(I)

B(5-A3A, 5-A3B, 5-B1B, 7-H, 10-A4, 10-A8, 10-A10, 10-A13D, 10-A15, 10-A18, 10-A19, 10-B1A, 10-B2B, 11-C7B5, 12-C10, 12-G1, 12-K4A5)

U, V, W, X, Y, Z = H, halo or 1-4C alkyl or 1-4C alkoxy (both opt. substd. by halo and/or OH), 1-6C heterocycle, 1-4C thioalkyl, NR_3R_4, $-R_5-A-R_6$, -A-R_7, CN, SO_2R_8, $NHCONH_2$ or $CONR_3R_4$;

R_1-R_4 = H or 1-4C alkyl;

R_5, R_6 = 1-6C alkyl;

R_7 = H, 1-6C alkyl, 1-6C heterocycle or -A-R_5;

R_8 = 1-4C alkyl or NR_3R_4;

A = S, NH or O;

provided that at least one of U-Z = halo.

Intermediate cpds. of formula (II) (see "Preparation") are also new.

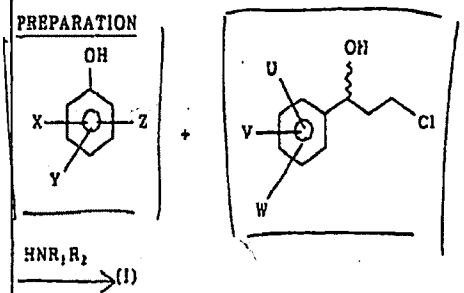
USE

(I) bind to neurotransmitter reuptake sites and esp. inhibit serotonin reuptake. Radioactive halogen (esp. ^{123}I) labelled cpds. of (I) are useful for imaging serotonin receptors using single photon emission tomography (SPECT) to assess and improve treatment of psychiatric disorders. (I) may also be useful for in vitro binding studies and as therapeutic agents.

SPECIFICALLY CLAIMED

N-methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine (Ia).

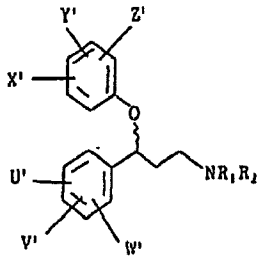
PREPARATION



HNR_1R_2 → (I)

Radioactive I-labelled cpds. of (I) are prepd. by treating the corresp. Br-cpd. with Et_3N/tetrakistriphenylphosphine palladium, then stirring the resulting tributyltin deriv. (IIa) with $I_2/CHCl_3$ or NaI/H_2O_2(aq.).

Other intermediates within the scope of (II) may be used to prepare the radiolabelled cpds. in an analogous manner.



(II)

one of U', V', W', X', Y', Z' = $Sn(R)_3$, $Si(R)_3$ or HgR and the others are as defined for U-Z;

R = 1-5C alkyl.

EXAMPLE

A mixt. of (R)-(+)-1-chloro-3-phenyl-3-(4-iodo-2-methylphenoxy)propane (0.58 g), aq. $MeNH_2$ (40%, 4 ml) and EtOH (1.5 ml) was heated at 130°C for 3 hr. in a sealed tube and worked up to give 0.25 g (44%) (R)-(-)-(Ia) α^{25}_D = + 11.98 (c 3.32, $CHCl_3$); HCl salt had m.pt. 68°C, α^{25}_D = -8.34 (c 0.82, $CHCl_3$).

In in vitro competitive binding assays using rat brain tissue prepn. (Ia). HCl had Ki 5 nM (serotonin uptake, (^{3}H-paroxetine)) and IC_{50} 20 nM (norepinephrine uptake, (^{3}H-nisoxetine)). (26pp2218AFDwgNo0/3).

SR:No-SR.Pub

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